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August 27, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-0529; Draft Guidance for Industry on Changes to an Approved NDA or ANDA; Notice of Availability and Request for Comments; Federal Register, Monday, June 28, 1999 (64FR34660); and

Docket No. 99N-0193; Supplements and Other Changes to an Approved Application; Proposed Rule; Federal Register, Monday, June 28, 1999 (64FR34609)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal business in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on these FDA proposals.

General Comments

The Agency is to be commended for their continuing efforts in providing the regulated industry with their current views and guidance on requirements pertaining to pharmaceutical products. This effort could be further enhanced at the time of issuing the final guidance by the provision of comments received by the Agency and their subsequent evaluation. This document could resemble the preamble to the final Rules as published in the Federal Register. Use of this technique would allow industry further insight into the concerns and viewpoints of the Agency on these important topics. This would also fulfill the spirit of FDAMA.

99N-0193

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It appears that the Agency has over utilized section 506A (c)(2)(c) in its translation of the Act to regulation and guidance. Consequently, so many changes have been deemed by the Secretary to have substantial potential to adversely affect the safety or effectiveness of the drug that the extent of reform envisioned by Congress is all but eliminated.

As the Modernization Act seeks to decrease the regulatory burden and recommends amendments to the CFR regulations, this guidance seems premature. The suggested changes in the regulations have not been made, so provision of the guidance may be construed as an effort to maintain the status quo by the Agency. As we are sure this is not the Agency's intent, the implementation of this guidance should be delayed until the current regulations have been amended.

314.70 Regulation Comments

To an extent extra burdens are imposed by:
314.70 (b)(2)(iv) - any change to impurity profile of bulk drug requires PA supplement. Removing hazardous solvents or otherwise improving the impurity profile requires same review/data as a change making profile worse. Thus it appears that all changes are considered in a negative light.

314.70 (b)(3)(viii) - all supplements require a reference list of SOPs - such listing is not required in original NDAs. Such listing is not relevant to the stated purpose for review. "When applicable" is not defined.

314.70 (c) (2) (ii) (A) - applies to both an increase or decrease in batch size involving new equipment. How does new equipment compare to replacement?

314.70 (d)(2)(i) - annual report can only include spec changes to conform to compendia where the change ALSO provides increase assurance of quality. The word "and" is restrictive.

314.70 (b)(3)(vii) - the inclusion of validation protocol for sterilization assurance is new. Further, submitting all validation data is different from data summaries previously requested and provided for microbiological consults.

Guidance Comments

"**Validate the effects of the change,**" means to assess the effect of a manufacturing change on the product. It does not mean, in this sense, to demonstrate reproducibility, and therefore is also going to confuse. A different word, possibly "*demonstrate*" would seem a better choice.

Comparability protocol, to be submitted to demonstrate the specific tests and validation studies that will be performed to assure acceptability of comparability between the old and new processing, may become contentious and delay approvals unless clearly defined.

The new regulations would require **prior approval** for component sterilization process changes or revised steps in an aseptic processing operation. This may delay implementation of improved measures.

Specific Comments

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The Agency should be commended in their effort to standardize, between divisions the criteria for expedited review. We think expedited review when delay in making a change that may impose an extraordinary hardship on the applicant will be very valuable to the industry. However, other criteria should apply such as when vendors can no longer supply key components or intermediates.

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We would suggest that the regulations and the guidance be changed to indicate that the changes be completely described in the "Basis for Submission" section and must be included in the cover letter only if such a section is not included in the supplement. This will allow better presentation of the proposed changes.

We would suggest that promotional labeling be allowed a phase in period of "at the time of next printing or within 6 months of a package insert change, whichever is sooner."

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Although the Agency contemplates the potential for a company to produce a product that has an adverse impact on the product quality, we believe they should address the potential for a company to improve the quality of a product. This is seen with improved raw material manufacturing producing less impurities or enhanced packaging such as introducing an innerseal for improved packaging. We feel these are more common than the FDA cited example.

We challenge why packaging site changes for controlled products, inhalers, nasal pumps, etc., is considered a MAJOR Change. The product is not being changed and the product is not affected by where it is placed into the container. Container integrity should sufficiently support the change.

Why are controlled release solids more restricted. If anything they are less affected by primary packaging than the other types of products.

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As SUPAC allows for such changes without prior approval, the sentences should read "Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application may be considered major changes..." We also believe that the FDA should change the guidance and the corresponding regulation (21 CFR 314.70 (b)(i)) to allow for the relaxation of drug product specifications WITHOUT prior approval if the change corresponds to a change in the USP.

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The Agency should consider a CBE supplement when the controls employed are increased rather than looking at all changes as prior approval supplements. For instance if air handling and/or barriers are erected in a manufacturing site that decrease the potential for cross-contamination, these should be allowed for as CBEs or annual report items.

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As a move on the same campus or different campus covers all possibilities, the statements would be clearer by just indicating a move to a different site.

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The Agency assumes that the applicant knows of critical product parameters and yet does not test for them. The approval process is supposed to identify the critical parameters to evaluate to determine if the process is in control whether or not the process is being changed. The Agency has concurred with the applicant that all of the critical parameters have been identified at the time of approval. Therefore this section should be deleted from the guidance as it implies the Agency is currently improperly approving applications.

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Changing the order of addition of ingredients does not always effect the drug product. The guidance should acknowledge this fact and allow Agency consultation concerning such an instance rather than requiring prior approval. There is normally little or no change when engraving, etc. are changed on a tablet, no matter whether IR or CR. This should also be Annual Report assuming satisfactory comparative dissolution studies for CONTROLLED RELEASE products are completed.

How does deletion of a piece of equipment increase the potential for contamination?

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This could be interpreted that changes in the manufacture of the drug substance that deal with recrystalization to improve purity or washing of the crystals to decrease solvents require prior approval. We believe the Agency should allow for such process improvements.

This implies that a listing of ingredients that are CDER approved will be made available from the Agency. As the Office of Generic Drugs has recently deleted their inactive ingredient guide, there is no current source for such information.

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This section should be revised to indicate that should the USP change or delete an analytical procedure prior approval is not needed as section 501 (b) of the Act legally recognizes the authority of the USP in analytical procedures and specifications for monographed items.

Additionally the section should be changed to indicate the once official monographs are accepted for non-LISP articles the applicant can change to the USP methods.

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This should not be MAJOR for Drug Substance unless primary container contains drug when product is sterilized. If product and container are sterilized separately, then data showing container integrity on stability seems to be sufficient and a CBE would seem appropriate.

We agree the ability to change the cap and liners on liquids with only an ANNUAL Report is justifiable relief.

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We would recommend that changes in desiccants also be allowed when they have been shown to absorb as much or more moisture than the current approved desiccant.

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We commend the approach in defining of Multiple Changes to use the one most restrictive and not make multiple change automatically a MAJOR prior approval change.

BMS appreciates the opportunity to provide comment and respectfully requests the FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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